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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|-------------|----------------------|---------------------|------------------|
| 10/781,850 | 02/20/2004 | Stevan P. Tofovic | 007278-04 | 1648 |
| 36234 | 7590 | 02/24/2006 | EXAMINER | |
| JENNIFER M MCCALLUM, PH D, ESQ THE MCCALLUM LAW FIRM, LLC 685 BRIGGS STREET PO BOX 929 ERIE, CO 80516 | | | HUI, SAN MING R | |
| | | | ART UNIT | PAPER NUMBER |
| | | | 1617 | |

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|-------------------------------|--------------------------------|--|
| Office Action Summary | Application No. 10/781,850 | Applicant(s) TOFOVIC ET AL. | |
| | Examiner San-ming Hui | Art Unit 1617 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 28 November 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-36 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicant's amendments filed November 28, 2005 have been entered. Claims 1-36 are pending.

The outstanding rejection under 35 USC 112, first paragraph is withdrawn in view of the amendments filed November 28, 2005 as the claims no longer recite "estradiol metabolites".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 7, 11, 15, 19, 23, 27, 31, and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The limitation "prodrug of estradiol metabolite" recited in the claims renders the claims indefinite because it is not clear what compounds are encompassed by the claims. In other words, it is not clear what compounds are considered as "prodrug of estradiol metabolite".

Response to Arguments

Applicant's arguments filed November 28, 2005 averring the term prodrug being well-known and understood by one of ordinary skill in the art have been fully considered but they are not persuasive. Examiner notes that the scope of the claims cannot be

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ascertained and the understanding of the term "prodrug" *per se* does not define the scope of the instant claims. The meaning of the term "prodrug" may be known; however, when such term is recited in the instant claims, the issue would be what compounds would be considered as a prodrug of the estradiol metabolites? The scope is not defined since no structural or chemical characteristics are associated with the term "prodrug".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over US2003/0027751 ('751) and US2001/0056068 ('068).

'751 teaches 2-methoxyestradiol as useful in treating pulmonary hypertension (See paragraph [0175] and [0179]).

'068 teaches the method of treating pulmonary hypertension (a nitric oxide deficiency disorder) using estradiol, estriol and estrone (See claims 1, 7, 14, and 16). '068 also suggests the use of continuous or prolong release dosage form (See paragraph 0119). Examiner notes that estradiol is a prodrug of estradiol metabolite.

The primary references do not expressly teach both 2-methoxyestradiol and estradiol be used together in the method of treating pulmonary hypertension.

It would have been obvious to one of ordinary skill in the art at the time of invention to employ both 2-methoxyestradiol and estradiol be used together in the method of treating pulmonary hypertension.

One of ordinary skill in the art would have been motivated to employ both 2-methoxyestradiol and estradiol be used together in the method of treating pulmonary hypertension. Concomitantly employ both agents, which are known to be useful in treating pulmonary hypertension, in a single method of treating the very same disorders would be *prima facie* obvious (See *In re Kerkhoven* 205 USPQ 1069). Examiner notes that the resulting mechanism of estradiol metabolites recited are considered as intrinsic properties within the metabolites of estradiol.

Response to Arguments

Applicant's arguments with respect to claims 1-36 have been considered but are moot in view of the new ground(s) of rejection.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to San-ming Hui whose telephone number is (571) 272-

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0626. The examiner can normally be reached on Mon 9:00 to 1:00, Tu - Fri from 9:00 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, PhD., can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


San-ming Hui
Primary Examiner
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